UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/484,964	01/18/00	YEH	E UTSH.248

HM22/0928

FULBRIGHT & JAWORSKI, LLP
600 CONGRESS AVE
SUITE 2400
AUSTIN TX 78701

EXAMINER	
BECKERLEG,A	
ART UNIT	**PAPER NUMBER**
1632	10

DATE MAILED: 09/28/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

PTO-90C (Rev. 2/95)

*U.S. GPO: 2000-473-000/44602

Office Action Summary	Application No. 09/484,964	Applicant(s) YEH, EDWARD T. H.	
	Examiner Anne M Beckerleg	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *73-101* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *73-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 January 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 73-84, 86-101 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The applicant claims methods of inhibiting apoptosis by introducing a nucleic acid sequence encoding a human sentrin-1 polypeptide. The applicant further claims said methods wherein the human sentrin-1 polypeptide is at least 85% or 95% identical to SEQ ID NO:2 or wherein the polypeptide comprises at least 20 or 30 or 40 or 50 or 60 or 70 or 80 or 90 or 100 contiguous amino acids of SEQ ID NO:2. The applicant also claims methods of inhibiting apoptosis by introducing a nucleic acid which comprises at least 50 or 100 or 200 nucleotides of SEQ ID NO:1.

The specification does not provide a sufficient written description for a human sentrin-1 gene or polypeptide which has a nucleotide sequence other than SEQ ID NO:1 or an amino acid

sequence other than SEQ ID NO:2. While the specification discloses several properties of the human sentrin-1 protein (SEQ ID NO:2) encoded by SEQ ID NO:1, such as the ability to bind to Fas, TNFRI, or UBC9, the specification does provide sufficient guidance as to the nucleotide or amino acid sequences, or the physical or structural properties of any gene or protein which shares these properties. Further, the specification fails to provide guidance as to the amino acid residues which are critical to the observed biological activities of the protein corresponding to SEQ ID NO:2 such that amino acid sequences or nucleotide sequences which diverge from SEQ ID NOS: 1 or 2 and which encode a human sentrin-1 polypeptide can be determined from among the numerous possible nucleotide or amino acid sequences which encode a portion of SEQ ID NOS:1 and 2. In particular, it is noted that SEQ ID NO:1 contains over 1100 nucleotides which are apparently non-coding sequence. The specification provides no guidance as to how any 50, 100, or > 200 nucleotide portion of the noncoding sequence of SEQ ID NO:1 can encode for a human sentrin I polypeptide, or provide any description of any nucleotide sequence corresponding to the non-coding sequence of SEQ ID NO:1 which meets the claim limitations of encoding a human sentrin-1 polypeptide. A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. See Oka, 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to

define it solely by its principal biological property, e.g., encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred. Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). Further, *Vas-Cath Inc. V. Mahurkar,* 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of 'written description' inquiry, whatever is claimed" (see page 1117). By failing to identify any nucleotide or amino acid sequence other than SEQ ID NOS: 1 or 2 which either encode a human sentrin-1 polypeptide or which have identical biological properties to the human sentrin-1, the specification does not "clearly allow persons or ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). Adequate written description requires more than a mere statement that an element is part of the invention. Based on the applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acid sequences which may be capable of producing a human sentrin-1 polypeptide, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel,* 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016. Applicant is

reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

Claims 73-101 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting Fas or TNFRI mediated apoptosis in cells in vitro comprising transfecting said cells with a nucleic acid expression construct encoding a nucleic acid comprising SEQ ID NO:1, does not reasonably provide enablement for methods of inhibiting any apoptotic pathway in cells in vitro or in vivo by administering any vector encoding any portion of the nucleic acid or amino acid sequence of SEQ ID NO:1 or SEQ ID NO:2 respectively. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims .

The applicant claims methods of inhibiting apoptosis by introducing a nucleic acid sequence encoding a human sentrin-1 polypeptide. The applicant further claims said methods wherein the human sentrin-1 polypeptide is at least 85% or 95% identical to SEQ ID NO:2 or wherein the polypeptide comprises at least 20 or 30 or 40 or 50 or 60 or 70 or 80 or 90 or 100 contiguous amino acids of SEQ ID NO:2. The applicant also claims methods of inhibiting apoptosis by introducing a nucleic acid which comprises at least 50 or 100 or 200 nucleotides of SEQ ID NO:1. The specification discloses a nucleotide sequence (SEQ ID NO:1) which is given the name human sentrin-1. The specification states that predicted human sentrin-1 polypeptide has

homology to ubiquitin and other ubiquitin-like proteins, particularly to the yeast Smt3 protein. The specification further provides evidence that the protein product of SEQ ID NO:1 appears to localize to the nucleus and can bind to several different proteins including Fas and TNFRI. The applicants further demonstrate that the transfection of a human cell line with the full length SEQ ID NO:1 inhibits apoptosis in response to anti-Fas or TNF.

The specification does not provide an enabling disclosure for inhibiting any apoptotic pathway in any cell in vitro or in vivo using any portion of a human sentrin-1 polypeptide or the full length human sentrin-1 nucleic acid or polypeptide. The art at the time of filing teaches that several different apoptotic pathways exist in the cell which can be triggered by substantially different stimuli (Lavin et al. (1996) Experimentia, Vol. 52, page 983, Figure 1; and Lieberthal et al. (1996) Am. J. Phys., Vol. 271 (3 part 2), page F483, column 1, paragraph 2). The specification teaches that while human sentrin-1 can bind to the death domains of Fas and TNFRI, it does not bind to CD40 or FADD/MORT1 (specification, page 53, lines 25-29). While the specification does provide additional working examples which disclose the ability of sentrin-1 to bind to various other proteins, such as UBC9, ranGAP1 or PML, it does not provide any evidence that this binding results in the inhibition of apoptosis in a cell. The specification suggests that sentrin interacts with these protein in a process similar to ubiquitination. Neither the specification nor the art at the time of filing teaches that the process of protein ubiquitination results in the inhibition of apoptosis. At the time of filing, it was well known that protein ubiquitination usually results in protein degradation. Thus, in view of the numerous different apoptotic pathways, applicant's

demonstration that sentrin-1 does not bind to FADD/MORT1 or CD40, the lack of correlation between the binding of sentrin to UBC9 , ranGAP1 or PML and any effect on apoptosis, and the breadth of the claims, it would have required undue experimentation to practice the scope of the instant invention as claimed and the skilled artisan would not have predicted success in inhibiting any apoptotic pathway in a cell by providing the cell with a nucleic acid encoding human sentrin.

The specification does not provide an enabling disclosure for the inhibition of Fas or TNFRI induced apoptosis in any cell in vitro or in vivo using any portion of a human sentrin-1 nucleic acid or polypeptide. The specification, as discussed above, provides evidence that the full length human sentrin -1 nucleic acid sequence encodes a polypeptide which when expressed in a murine or human cell is capable of inhibiting to a greater or lesser degree Fas or TNFRI mediated apoptosis. The specification, while disclosing that portions of the nucleic acid sequence of a human sentrin or specifically of SEQ ID NO:1 can be used to inhibit apoptosis, does not provide sufficient guidance as to which portions, of the numerous possible nucleic acid sequences which may comprise 50 or more contiguous nucleotides of SEQ ID NO:1 or which may encode 20 or more contiguous amino acids of SEQ ID NO:2, retain the apoptosis inhibiting activity of the full length human sentrin -1 polypeptide, SEQ ID NO:2, encoded by SEQ ID NO:1. In regards to the nucleic acid sequence in SEQ ID NO:1, it is noted that first 90 and the last 1065 nucleotides of SEQ ID NO:1 do not apparently encode for any polypeptide. If any open reading frame exists in the first 90 nucleotides or the last 1065 nucleotides, the specification neither discloses the corresponding encoded amino acids or provide any guidance as to the nature or activity of any

hypothetically encoded polypeptide. The specification further does not provide any guidance that the non-coding nucleotides of SEQ ID NO:1 have any anti-apoptotic activity. As the specification teaches that the anti-apoptotic activity of the human sentrin 1 polypeptide comprising the amino acid sequence of SEQ ID NO:2 is the result of protein:protein interactions, the skilled artisan would have considered it highly unpredictable whether any 50 or 100 or 200 contiguous nucleotides from the non-coding portion of SEQ ID NO:1 would have any effect on apoptosis in a cell. In addition, the specification, while suggesting that a nucleic sequence encoding any 20 up to 100 contiguous amino acids of SEQ ID NO:2 can be used to inhibit apoptosis according to the instant methods, Figure 1A demonstrates that only the full length sentrin corresponding to the entire 101 amino acids of SEQ ID NO:2 can bind to the Fas death domain. The 1-70AA sentrin fragment and the 1-23AA sentrin fragment failed to exhibit Fas binding (specification, Figure 1A). The specification does not provide any specific guidance as to the amino acid sequence of any 20 or 30 or 40 or 50 amino acid portion of SEQ ID NO:2 which retains Fas or TNFRI binding and which is further capable of inhibiting apoptosis in a transfected cell expressing said portion. The results of Figure 1A indicate that amino acid residues 71-101 of SEQ ID NO:2 are clearly required for Fas binding. In the absence of specific guidance from the specification and in view of the results depicted in Figure 1, it is unclear which residues are essential for Fas or TNFRI binding and apoptosis inhibition and thus, the skilled artisan would not be able to predict whether any portion of the amino acid sequence of SEQ ID NO:2 would be capable of retaining the apoptosis inhibiting activity of the full length human sentrin-1 protein. Further, as discussed in the previous

paragraph, while the specification provides data concerning the binding of sentrin-1 to various proteins other than Fas or TNFRI and provides some analysis of sentrin domains required for binding to UBC9 , ranGAP1 or PML, the specification has not related the "sentrinization" of these proteins with any effect on apoptosis. Thus, in view of the failure of the 1-70AA and 1-23AA portions of sentrin-1 to bind to Fas, the lack of guidance concerning specific portions of the sentrin polypeptide which retain Fas and/or TNFRI binding and anti-apoptotic activity, the lack of correlation between applicant's binding studies of sentrin to UBC9 , ranGAP1 or PML and any effects on apoptosis or sentrin binding to Fas or TNFRI, and the breadth of the claims, the skilled artisan not have been able to predict without undue experimentation whether any portion of SEQ ID NO:1 or a nucleic acid sequence encoding any portion of SEQ ID NO:2 would be capable of inhibiting Fas or TNFRI mediated apoptosis.

The specification does not provide an enabling disclosure for inhibiting apoptosis in vivo by directly administering any vector encoding human sentrin-1. The specification discloses that a pharmaceutical composition comprising a nucleic acid encoding sentrin-1 can be administered to a mammal in order to inhibit apoptosis. The specification does not disclose any disease or condition associated with apoptosis. Further, the specification fails to provide any guidance concerning the characteristics of cells to be targeted for apoptosis inhibition, the level of sentrin expression from any vector in such a target cell which correlates with apoptosis inhibition, the routes and dosages of administration of any vector encoding sentrin to a mammal such that the target cells or organs are transfected, or the level and duration of apoptosis inhibition within a

target cell population which correlates with any effect on any symptom of an apoptosis related disease or condition. At the time of filing, in vivo gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or adeno-associated viruses, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, ".. difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1). Orkin et al. further states in a report to the NIH that, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2). Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, and the identity of the promoter used to drive gene expression. Thus, the art at the time of filing clearly establishes that the expectation for achieving a desired therapeutic effect in vivo by expressing a

therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low. Therefore, in view of the art recognized high level of unpredictability in treating disease using recombinant vectors at the time of filing, the lack of guidance provided by the specification for the parameters affecting vector delivery and gene expression in vivo, the lack of correlation between applicant's in vitro working examples and the therapeutic inhibition of apoptosis in a mammal, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

The claims are free of the prior art of record for the following reasons. While the prior art does teach nucleic acids and proteins which the specification discloses are identical to the human sentrin 1, see for example PIC1 described by Boddy et al. (1996) (PTO-1449, C1), the prior art of record does not teach or provide motivation for using these sequences to inhibit apoptosis.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 8:30-6:00. General inquiries should be directed

to the group receptionist whose phone number is (703) 308-0196. The art unit fax number is (703) 308-8724.

Dr. A.M.S. Beckerleg

A.M.S. BECKERLEG
PATENT EXAMINER